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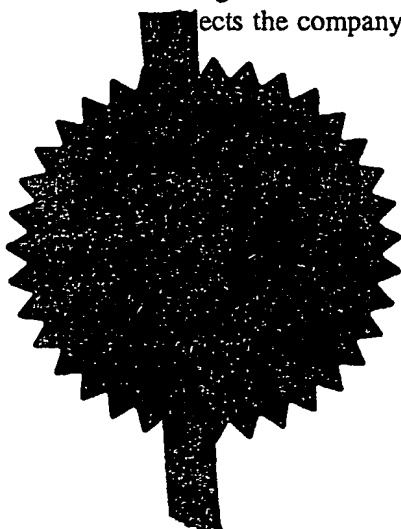
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P. Mahoney

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Request for grant of a patent

The Patent Office
Cardiff Road
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Gwent NP9 1RH

1. Your reference

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2. Patent Application Number

9827006.9

3. Full name, address and postcode of the or of each applicant (names)

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58.30.12 0002

Patents ADP number (if known)

If the applicant is a corporate body, give the
country/state of its incorporation

Country: NETHERLANDS ANTILLES
State:

4. Title of the invention

PHARMACEUTICAL COMPOSITIONS

5. Name of agent

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6. Priority details

Country

Priority application number

Date of filing

152600
Lucas 2
135 Waltham
Warlingham
Surrey
C20 2H
Form 5.17

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Patents Form 1/77

7. If this application is divided or otherwise derived from an earlier UK application give details

Number of earlier of application

Date of filing

8. Is a statement of inventorship and or right to grant of a patent required in support of this request?

YES

9. Enter the number of sheets for any of the following items you are filing with this form.

Continuation sheets of this form .

Description 10 /

Claim(s) 2 / 2

Abstract 1 /

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and
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Request for preliminary examination
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Request for Substantive Examination
(*Patents Form 10/77*)

Any other documents
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11. I/We request the grant of a patent on the basis of this application

Signature



Date 8 December 1998

BÉRESFORD & Co

12. Name and daytime telephone number of person to contact in the United Kingdom
PAUL COLE
Tel:0171-831-2290

PHARMACEUTICAL COMPOSITIONS

Field of the invention

The present invention relates to the preparation of carriers for both lipophilic and hydrophilic compounds. More specifically, it relates to the formation of an improved carrier
5 for these compounds by utilising membrane lipids, particularly phospholipids to improve bioavailability, increase efficacy and reduce toxicity. The invention also relates to the preparation of novel phospholipid carriers that have improved physical properties and loading capacity, thereby providing the means to produce novel dosage forms.

Background to the invention

10 Poor and/or unpredictable bioavailability, resulting in minimal uptake of the pharmacologically active compound (PAC) into the target organ and/or systemic circulation, is a major problem of drug therapy. In this context, bioavailability refers both to the transport of a compound across a semi-permeable biological membrane or cell and/or uptake into the systemic circulation. Poor bioavailability may be due to:

15

- (i) lack of solubility in aqueous media and/or
- (ii) incapacity of the molecule to cross the cell membrane.

The problem is especially significant in the case of poorly water-soluble, hydrophobic
20 PACs and presents a major challenge in formulation development, in which the objective is to achieve maximum bioavailability. In some instances it may be possible to improve the water solubility of an active compound by forming a chemical derivative that is more hydrophilic without bringing about an unacceptable change in the pharmacokinetics of the compound. However, this invention is concerned with the alternative approach where the chemical
25 identity of the compound is or has to be left unchanged.

It is difficult to find carrier systems that can solubilise water-insoluble PACs and that

are non-toxic for oral administration. Ethanol and ethoxylated surfactants are conventionally employed for this purpose although there are serious limitations on their use. Another approach towards improving solution of hydrophobic PACs is to present the active material in a colloidal form or as a co-precipitate with the aim of improving dissolution kinetics. 5 However, this approach does not completely solve the problem because although increased solubility may be achieved, bioavailability is frequently poor.

The problem of poor bioavailability is not limited to hydrophobic PACs. Some hydrophilic compounds with large molecular weights may also present similar problems. Examples of hydrophilic PACs which are poorly absorbed include polypeptides e.g. insulin, 10 and genetic material e.g. oligosense nucleotides, etc. Poor bioavailability in these compounds is believed not to be due to lack of solubility, but instead to do with difficulties in transport across the mucosal membrane.

Phospholipids generally and liposomes in particular, are recognised to be useful carriers for PACs. However, major problems associated with stability, physical characteristics, 15 cost, and PAC carrying capacity have limited their use. The use of diacyl phospholipids alone, essentially in the form of liposome dispersions to carry PACs, particularly lipophilic compounds, is exhaustively described in the prior art. The type of liposomes employed include SUVs, MLVs, REVs, SPLVs, etc. It is well known that commercialisation of liposome drug delivery systems has been seriously hampered by poor stability, inadequate loading capacity, 20 requirement for purified lipids and expensive production methods.

Co-pending application PCT/GB98/01803 describes lipid compositions comprising at least one micelle forming lipid eg monoacyl phospholipid and mixtures of mono acyl and diacyl phospholipids which are effective in carrying lipophilic compounds in molecular form. The compositions may be a waxy solid, a paste-like material or a viscous fluid suitable for 25 filling into hard or soft gelatine capsules.

The preparation of solid lipid-drug co-precipitates using diacyl phospholipids to increase the dissolution behaviour of poorly water soluble drug solvates, and the possibility of modifying drug release from such dispersions by incorporating small amounts of polymers,

has been described in *J. Pharm. Sci.* 81, 283-286 (1992). The compositions were prepared essentially by co-precipitation and resulted in the incorporation of lipid in the crystalline structure of the solvate. The residual solvent trapped in the solvates may be one reason for the improved solubility of the poorly water soluble compound.

5 PCT/US86/00637 discloses the use of non-esterified fatty acids and monoglycerides together with minor amounts of a monoacyl lipid (lyso phosphatidylcholine) to form lipid particles which show improved oral absorption for various lipophilic compounds. Improved oral absorption is alleged to be due to the unique properties in the combination.

Enhanced bioavailability of hydrophilic molecules has also been reported using
10 medium chain triglycerides in W/O micro emulsions, see *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 22 (1995).

The use of enzyme modified lecithin containing both monoacyl and diacyl lipids as emulsifiers is well known. These phospholipids are widely employed to stabilise dispersed phase systems particularly in food technology but have not previously been used as carriers
15 for PACs.

The prior art concerning monoacyl phospholipids mainly describes the ability of micellar solutions to disrupt membranes. EP-B-0 256 090 claims the use of a particular monoacyl lipid ie. lyso-phosphatidylethanolamine alone or in combination with other diacyl phospholipids to solubilise hydrophobic materials in liposomal SUV suspensions. As far as
20 the applicants are aware, the use of monoacyl phospholipids, particularly hydrolysed lecithin allowed for food applications, to form lipid associates with bioactive compounds in unit dose solid formulations has not previously been described.

Summary of the invention

The primary objective of carrier systems is to achieve maximum bioavailability with
25 minimum side-effects. An object of the present invention is to provide an improved carrier for both lipophilic and hydrophobic PACs that is safe, efficient and effective and may provide

broad pharmaceutical utility and clinical benefits.

The present invention uses defined lipid compositions to form solidified lipid associates with water-soluble and oil-soluble compounds, thereby avoiding the serious limitations inherent in liposomes which have restricted their commercialisation. It can provide
5 membrane lipid complexes eg. phospholipid associates formed with hydrophobic and hydrophilic PACs that have improved bioavailability and may be formulated into a variety of unit dosage forms. Depending on the route, improved absorption may take place in the GI tract after oral administration, or across buccal and other mucosal surfaces when the lipid associates are formulated as lozenges, pessaries and suppositories.

10 The present invention is concerned with solid and granular compositions containing PACs which can be either hydrophilic or lipophilic and need not be in molecular dispersion. The PAC may be either in discrete, micro-fine/colloidal dispersion in a solid lipid matrix or exist as a lipid associated micro-fine powder where the lipid physically adheres to the solid drug particles.

15 The invention provides lipid associates in solid dosage forms, comprising mixtures of at least one micelle forming monoacyl lipid and/or at least one bilayer forming diacyl lipid. The active compound may be in molecular solution in the lipid or lipid mixture or it may be present as a discrete micro-fine dispersion. Preferably a polymer is also present to retain the composition at the membrane surface and thus enhance absorption. However, the need for
20 a polymer to be present in order to convert a waxy lipid material to a comminutable form does not arise where a small amount of lipid is physically adhered to the surface of particles of the active compound to give a free-flowing powder that readily disperses in water.

Description of preferred embodiments

We have found that mixtures of membrane forming lipids and micelle-forming lipids
25 have a number of advantages for the administration of pharmaceutically active compounds. These advantages include improved dispersibility in water, so that a readily dispersible

composition may be made by forming a suspension of a hydrophobic PAC containing the lipid mixture in a minor amount by weight e.g. 1-20% by weight, typically about 10% by weight, and removing the solvent to produce the PAC coated with or physically adhered to the minor amount of lipid mixture.

5 We have found that membrane lipids, especially phospholipids, can act as natural carriers by forming lipid associates with PACs e.g. by physical adhesion, using defined, pure lipids or specified monoacyl and diacyl phospholipids. Preferred compositions contain at least one micelle forming lipid, preferably a monoacyl phospholipid in the mixture. We have found that compositions containing both a monoacyl phospholipid and diacyl phospholipid give rise
10 to improved bioavailability of a dissolved PAC irrespective of whether or not the active compound is dissolved in the lipid. This may be the result of any of

- (i) enhanced ability to effect molecular solution of poorly water soluble compounds,
- (ii) enhanced absorption of both hydrophilic and lipophilic compounds through lipid-membrane interaction and altered permeability, and
- 15 (iii) longer *in vivo* retention of the hydrated lipid associate on absorption surfaces.

In especially preferred compositions, polymeric compounds that are soluble in solvents for phospholipids or in the solution or dispersion of lipids, are optionally included to modify the swelling properties of the composition. Specifically, the polymer helps to retain the lipid aggregates on membrane interfaces by controlling hydration, thereby prolonging lipid-
20 membrane interaction for maximum absorption. On a practical level, the inclusion of a polymer renders the lipid-associate even more friable, allowing it to be more easily broken up into granules for filling into hard gelatine capsules or compacted into tablets. This surprisingly simple improvement allows natural unsaturated phospholipids that are normally sticky, to be more 'user-friendly' and facilitates commercialisation. It also allows larger
25 amounts of phospholipids to be used in formulations for carrying and improving the absorption of PACs. The lipid associate may be compacted, spheronised or converted into pellets or other appropriate unit dosage forms with the aid of fillers such as lactose.

The monoacyl lipid(s) is preferably the monoacyl derivative of a phospholipid, but it can also be the monoacyl derivative(s) of glycolipids, spingolipids, or another suitable micelle forming lipid. The lipids may be derived from natural plant, or animal or microbiological sources, synthesised or partially synthesised including polyethyleneglycol (PEG) derived
5 monoacyl phospholipids, eg. pegalated monoacyl phosphatidyl ethanolamine.

The diacyl lipid(s) is preferably a phospholipid. Examples of phospholipids are phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine and spingomylin. The acyl chain can either be unsaturated or saturated and can have between 12 to 22, preferably 14 to 18 carbon atoms. Other membrane lipids such
10 as glycolipids, ceramides, gangliosides and cerebroside can be used in place of, or partial place of, phospholipids.

Although pure fractions of the monoacyl or diacyl lipids may be used, preferably, the molar ratio of diacyl to monoacyl lipid, or other micelle forming amphipath in the mixture would normally be from 1:99 to 99:1, preferably between 1:25 and 25:1 and most preferably
15 1:10 and 10:1.

In practice, instead of mixing pure fractions of the two lipids to obtain the target ratios, partially enzyme hydrolysed mixtures of lecithin that have the required proportions of the monoacyl to diacyl components are preferred. These phospholipid mixtures, which are classed as lecithins are freely permitted in foods without restrictions and should thus present
20 no problems for oral use. Wherever possible hydrolysed lecithin containing from 10 to 80, preferably 60 to 80 mole percent of monoacyl phospholipids obtained by enzyme hydrolysis with phospholipase A2 is preferred.

The type of polymer when used, is preferably confined to materials that are soluble in solvents for the lipid eg. ethanol, isopropyl alcohol, n-propyl alcohol, dichloromethane,
25 THF, etc, and include the methacrylic resins sold as Eudragit, povidones, ethylcellulose, poly vinyl alcohol, polyvinyl acetate phthalate, etc. In some cases, water soluble polymers eg natural gums and modified starches may also be used as long as they are not incompatible with the lipid solution or dispersion and a small quantity of water is present initially in the lipid

composition to disperse the polymer prior to removal of solvent. The amount of polymer included may be between 1% to 50% or more, depending on the required hardness and hydration characteristics of the lipid associate. Normally, increased amounts of polymer result in harder and more friable compositions that are easier to break up. Furthermore, the use of
5 pH dependent acrylic polymers allow the required hydration and/or drug release profile to be obtained in the GI tract, thereby providing controlled drug release formulations in the GI tract. Alternatively, pH-independent polymers controlled mainly by swelling can be employed by using polymers that hydrate independent of pH eg povidones and certain methacrylic copolymers.

10 The type of PAC associated with the lipid may either be hydrophilic or lipophilic. These include eg. genetic material, proteins, macrolides, muranyl peptide, polypeptides, vaccines, insulin, calcitonin, etc. The amount and concentration of PAC in the composition depends on the dosage and is not an important feature of the invention. The quantity of lipid used to form the associate, however, depends on a number of considerations. These include
15 PAC concentration and solubility, bioavailability and related formulation requirements. For simple improvements in wettability and dispersion of water insoluble PACs, the amount of lipid can be as low as 1:99(lipid:drug) and normally the product is a free flowing powder. Where the invention is required to molecularly disperse water-insoluble PACs substantially, higher amounts of lipid would be required to form the associate. With highly lipophilic
20 compounds, lipid:drug ratios of 99:1 or more may be employed and the lipid associate formed has the characteristics of the bulk lipid. In most cases, lipid:drug ratios between 25:1 to 2:1 would be quite sufficient either to, i) substantially solubilise lipophilic PACs or ii) improve the bioavailability of both lipophilic and hydrophilic compounds by altering membrane permeability. As a rule, less lipid is required to molecularly disperse lipophilic PACs if higher
25 proportions of monoacyl fractions are used. In the case of more hydrophilic PACs that cannot be solubilised in the lipid mixture, the compound may simply be a dispersion in the lipid matrix. Following oral administration, the enhancement in bioavailability may also be due to the lipid associate having better retention on the absorption sites in the GI tract, thereby further increasing drug transport.

The invention will now be further described in the following examples.

Example 1

A solid associate containing cyclosporin A, phospholipid and a methacrylic acid copolymer was produced using a two stage process. The first stage involved dissolving 5 parts of lipid, 1 part of drug and 2 parts of polymer (Eudragit L100; Rohm) in a minimal quantity of ethanol. The lipid blend used in this formulation had a PC:MAPC weight ratio of approximately 33:66. The components were subjected to ultrasonication at 50°C until an optically clear ethanolic solution was obtained. The second stage involved removing the ethanol by vacuum drying for approximately 6 hours to produce a solid lipid-hydrophobe associate. The sample was weighed to a constant weight to ensure the complete removal of solvent from the associate with the cyclosporin A in molecular dispersion.

The resulting lipid-associate was a friable, light yellow solid, which could be broken down into lipid aggregates about 1-2 mm diameter. 25% by weight of micro crystalline cellulose (Avicel), a direct compression aid was used to produce a material that could be compressed into tablets which did not disintegrate in simulated gastric fluid.

Example 2

A solid associate containing cyclosporin, phospholipid and povidone was produced using the method described in Example 1. The required amounts of cyclosporin A (1 part by weight), lipid (5 parts by weight) and povidone (6 parts) were accurately weighed into a drying vessel. The PC:MAPC weight ratio of the lipid was approximately 33:66. The solid components were dissolved in a minimal amount of ethanol by ultrasonication at 50°C. The optically clear, yellow solution was vacuum dried to remove the ethanol. The resultant associate was a firm glass-like solid, which could be comminuted and was suitable for filling into hard gelatine capsules. The cyclosporin A was in molecular solution in the lipid.

Example 3

A nifedipine/phospholipid associate was produced by dissolving 1 part by weight of

nifedipine and 5 parts by weight of lipid (PC:MAPC weight ratio of 33:66) in a minimal amount of dichloromethane containing 2 parts by weight of a methacrylic copolymer (Eudragit L 100) at room temperature. The resultant solution was subjected to vacuum drying until no dichloromethane could be detected. The resultant yellow solid associate was kept in
5 the dark prior to hydrating in deionised water.

A dispersion was produced by adding 0.2 g of the solid-lipid dispersion to 10 ml of deionised water. The lipid-associate hydrated easily to give a homogeneous viscous solution where the nifedipine was substantially in solution and partially in suspension.

Example 4

10 A griseofulvin/lipid associate was produced by forming a slurry of griseofulvin in an ethanolic solution of lipid (PC:MAPC 98:1). The lipid:griseofulvin weight ratio of this preparation was 1:10. The ethanol was removed from the slurry by vacuum drying at 50°C for 6 hours. The resultant associate was an off-white flowable powder with a small amount of lipid physically adhered to the drug particles and could easily be wetted in aqueous medium
15 to form a homogeneous microfine suspension. A polymer need not be present in this formulation because the composition remains a flowable powder due to the small amount of lipid present.

Example 5

An associate containing griseofulvin, lipid (PC:MAPC weight ratio 33:66) and
20 methacrylic acid copolymer was produced by suspending the griseofulvin in an ethanolic solution of polymer and lipid. The griseofulvin:lipid:polymer weight ratio of this associate was 10:5:2.5. The lipid-drug suspension was vacuum dried for 6 hours at 50°C to remove the ethanol.

The resultant associate was an off-white flowable powder that may be compressed
25 into tablets or filled into hard gelatine capsules, although it had larger amount of lipid compared to Example 4 due to the inclusion of the polymer.

Example 6

A lipid associate containing lipid (PC:MAPC weight ratio 33:66):cyclosporin A methacrylic acid copolymer in the ratio 5:1:0.667 was prepared following the method in Example 1. A hard, waxy solid was obtained that could be broken into granules. The
5 powdered lipid associate remained in suspension in water below pH 6 and dissolved above pH 6. The cyclosporin A was in molecular solution.

The methods used for forming the lipid associates shown in the Examples employ simple vacuum drying at elevated temperature followed by a comminution process to break up the friable lipid aggregate into granules. Any appropriate process involving solvent
10 removal and/or production of particulate material would be suitable for scale up. These include spray-drying, lyophilisation, supercritical extraction, spray congealing.

CLAIMS

1. A composition for delivering a biologically active compound to a living organism, said composition comprising an effective amount of a pharmaceutically active compound dissolved or dispersed in a lipid and a polymer for modifying the swelling properties of the composition and/or for rendering the composition comminutable or friable.
2. The composition of claim 1, wherein the lipid is a membrane lipid, a micelle-forming lipid or a mixture thereof.
3. The composition of claim 2, wherein the monoacyl lipid and the diacyl lipid are present in a weight ratio of 1:99 to 99:1.
4. The composition of claim 2, wherein the monoacyl lipid and the diacyl lipid are present in a weight ratio of 1:25 to 25:1.
5. The composition of claim 2, wherein the monoacyl lipid and the diacyl lipid are present in a weight ratio of 1:10 to 10:1.
6. The composition of any of claims 3-5, wherein the monoacyl lipid and diacyl lipid are a mixture obtainable by enzyme hydrolysis.
7. The composition of any preceding claim, wherein the amount of polymer present is 1-50 wt% based on the weight of the composition.
8. The composition of any preceding claim, wherein the polymer is a methacrylic resin, a povidone, a cellulose derivative, a polyvinyl alcohol or polyvinyl acetate phthalate or is a gum.
9. The composition of any of claims 1-7, wherein the polymer is an acrylic polymer whose degree of swelling depends on pH.
10. The composition of any preceding claim in comminuted form, spheroidised form, pellet form or in the form of a tablet or capsule.

11. A substantially homogeneous composition comprising an effective amount of a pharmaceutically active compound and at least one micelle-forming lipid, the compound being at least partly in suspension on the lipid.
12. The composition of claim 11, wherein the compound is at least partly in suspension in a mixture of membrane lipid and micelle-forming lipid.
13. The composition of claim 11 or 12, wherein the compound is nifedipine.
14. A composition comprising a pharmaceutically active compound mixed or physically adhered to a minor amount of a micelle-forming lipid or of a mixture of a micelle-forming lipid and a membrane lipid.
15. The composition of claim 14, wherein the pharmaceutically active compound is griesofulvin.
16. The composition of claim 14 or 15, wherein the amount of lipid is 1-20 wt % based on the weight of the composition.
17. The composition of claim 14 or 15, wherein the amount of lipid is about 10 wt % based on the weight of the composition.

ABSTRACT

PHARMACEUTICAL COMPOSITIONS

A composition is provided for delivering a biologically active compound to a living organism. The composition comprises an effective amount of a pharmaceutically active
5 compound dissolved or dispersed in a membrane lipid, a micelle-forming lipid and/or a mixture thereof and a polymer for modifying the swelling properties of the composition and/or for rendering the composition comminutable or friable. The composition may be provided in comminuted form, spheroidised form, pellet form or in the form of a tablet or capsule. Alternatively there may be provided a composition in the form of a free-flowing powder or
10 a spheroid, pellet, tablet or capsule made therefrom, the composition comprising a pharmaceutically active compound mixed or physically adhered to 1-20 wt% of a micelle-forming lipid or of a mixture of a micelle-forming lipid and a membrane lipid. The invention also provides a substantially homogeneous composition comprising an effective amount of a pharmaceutically active compound and at least one micelle-forming lipid, the compound
15 being at least partly in suspension on the lipid.

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AGENT : Lucas & Co

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CANADIAN INTELLECTUAL
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(51) Int.Cl.⁶ A61K 47/24, A61K 47/44, A61K 9/20
(30) 1995/08/25 (19531277.5) DE
(54) **UTILISATION DE LIPIDES COMME ADJUVANTS DANS LA
FABRICATION DE FORMES MEDICAMENTEUSES SOLIDES
SELON LE PROCEDE D'EXTRUSION DE MATIERE FONDUE**
(54) **USE OF LIPIDS AS AIDS IN THE PRODUCTION OF SOLID
DRUG FORMS BY MELT EXTRUSION**

(57) L'invention concerne l'utilisation de lipides comme adjuvants dans la fabrication de formes médicamenteuses solides selon le procédé d'extrusion de matière fondue.

(57) Use of lipids as adjuvants in the production of solid medicinal forms by the melt extrusion process.



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